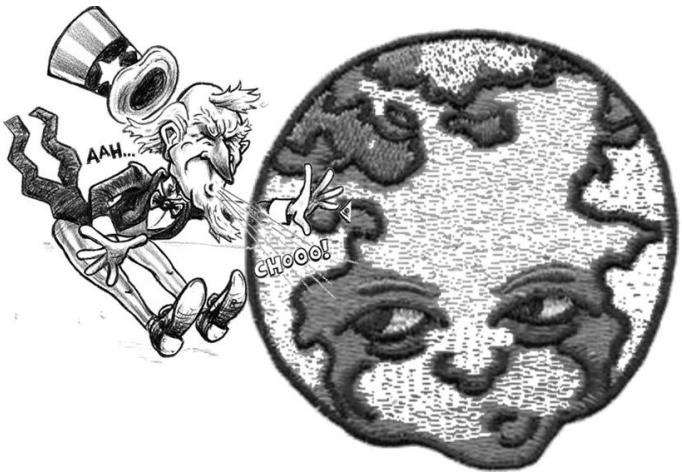
When the US sneezes the world catches a cold



This phrase tells us that, as a global leader, what happens in America will have an impact elsewhere. An example of this might be that in the wake of the 2016 election of Donald Trump, there have been other populist and nationalist leaders elected, including in Europe.

It has been the same with drugs policy since Richard Nixon's declaration of a 'War on Drugs' in 1969. There quickly followed US legislation to curb illicit drug use; the major concern being Vietnam Vets returning from 'Nam with heroin habits and (arguably racially motivated) concerns about cocaine and cannabis use. Soon much of the world signed up to this new war as a direct result of pressure exerted via US foreign policy. Predictably the UK followed suit with the Misuse of Drugs Act 1971.

The UK's Misuse of Drugs Act remains the major instrument governing drugs use, production, importation, supply, and associated legal penalties for such activities. It is a fairly clear example of catching a cold from Nixon's sneeze across the pond. It isn't a devolved matter either which means MLAs cannot amend it to suit local needs. For example in 2017 the Scottish Lord Advocate was unwilling to allow a Drug Consumption Room in Glasgow despite a glaring need there and local approval. He determined that this needed an amendment of the Act at Westminster, thus effectively removing it from Holyrood.

You may have watched Dr Michael Mosley's recent Horizon programme on what he feels has been a developing opioid crisis in the UK, arguing a comparison with the well documented opioid crisis in the US. It is worth noting that the programme focussed on chronic or persistent pain, that is, pain which continues beyond 3 or 4 months after an injury or surgery. It's focus is not primarily on illicit drug use or policy:

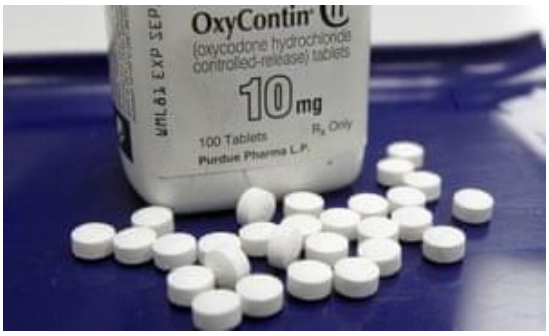
https://www.bbc.co.uk/iplayer/episode/m000dbpf/horizon-2020-1-addicted-to-painkillers-britains-opioid-crisis

The 1990s

Pharma companies in the US have long enjoyed the ability to market their produce with advertising direct to the public and by wooing would be prescribers. To us in the UK this seems odd; 'Ask your doctor for…..' Their regulatory body is paid for by these same companies and may well be more influenced by them than our own *independent* MHRA (Medicines and Healthcare products Regulatory Agency). That distinction is important when we consider how we have avoided the worst of the North American opioid epidemic.

Back in 1995 Dr. James Campbell in his Presidential Address to the American Pain Society, presented the idea of evaluating pain as a vital sign. Vital signs include temperature, pulse and respiration. By elevating pain to the level of essential information he hoped it would be properly evaluated and managed. This idea rapidly caught on rapidly across the US and then the rest of the world.

One pharma company in particular found a gap for pain medications which could alleviate this previously unassessed and possibly therefore, untreated pain. In that culture they could aggressively advertise direct to prescribers: Purdue Pharma's OxyContin, owned by the billionaire Sackler family. In 1996 Purdue sold $48m of this drug. By 2000 sales were over $1.1 bn. It must be noted however that even in the US powerful opioids were never advertised directly to the public.



OxyContin

OxyContin is a trade name for the drug oxycodone, a potent opioid with a duration of effect of 3-4 hours. Oxycodone was first produced in Germany in 1916. It has been available as a 'generic' (out of patent) and therefore, cheap medication for decades. Purdue found a way to delay the release of oxycodone so that 1 dose could be extended to give effective pain relief for up to 12 hours. Hence the oddly titled OxyContin stands for Oxycodone Continuous (delivery), explaining the capitalisation mid-word. As such it became a branded product, not a generic, and could be sold for a higher price as Purdue held the patent. The link below tells the story of the Sackler family who own Purdue in detail.

https://www.youtube.com/watch?v=zGcKURD_osM&feature=youtu.be

The perfect storm brewed; the emergence of pain as a vital sign and a new, aggressively marketed painkiller. Now non-cancer and non-acute pain was to be treated with a potent long-acting opioid.

Those with chronic or persistent pain were a vast and new market. They were about to add opioid dependence to their chronic pain. Even worse was to follow. It turns out that Purdue was lying about the benefits and risks of OxyContin. For example, to physicians who reported that their patients did not get 12 hour relief of their pain from taking OxyContin. Purdue told them to prescribe a higher dose. Or from physicians reporting that their patients were becoming 'addicted' to the drug. The Purdue answer; addiction is very rare. In fact both of these answers were untrue.

In some people opioid use seems to sensitise them to pain in the longer term. It is thought that the opioids prevent the body's natural ability to reduce pain as it might otherwise. Purdue's solution: Prescribe more OxyContin and add in a little OxyNorm for breakthrough pain between OxyContin doses. (OxyNorm is Oxycodone Normal delivery i.e. simple oxycodone.) By now someone could be taking 40mg OxyContin twice a day and perhaps another 20mg of OxyNorm over 24 hours. Next step, the physician ups the dose of OxyContin to 50mg twice daily. Then as their tolerance built to this increased dose their breakthrough pain would reappear requiring OxyNorm once again. And so on. This is known as 'dose escalation'.

Roots

These were the roots of the opioid epidemic that has caused so much misery in both the US and Canada. 'Pill mills' sprung up to service these new dependent opioid users. More and more stories abounded of people suffering from addiction, defined here as progressive loss of control over the use of a substance despite negative consequences. Dependence is a different concept and not the same as addiction. Dependence occurs when someone's use of a drug is sufficiently regular to cause withdrawal symptoms if the use stops. In the case of opioids a person develops tolerance to them over time, meaning that they need more to achieve the same (pain-killing) effect. Many users started to snort then inject the tablets until a reformulation of OxyContin in 2010 made this more difficult. Desperate people were escalating their tolerance to opioids as a direct consequence of Purdue's advice to prescribers to increase dose. Opioids work well for a short period of time but as we have seen above, the dose which previously managed pain soon no longer does the trick.

It is thought that beyond 120mg of morphine equivalence (MME) per day provides no better analgesia. A 30mg tablet of OxyContin taken twice daily is a total dose of 60mg oxycodone per day which is equivalent to the 120 MME. Yet OxyContin tablets come at up to 160mg tablets (320MME) which far exceeds the 120 MME limit even if taken once a day. Incidentally opioids are the only medication which if taken and no longer work are not discontinued and another approach or treatment tried. There is almost no ceiling to the tolerance you can achieve to opioids so you might have been on a huge dose of OxyContin with no better anaesthetic benefit than a much lower dose. In most drug use there is a principle that 'less is more'. The more you use, and the more often, the lower the reward. It's the law of diminishing returns.

Mother Morphine

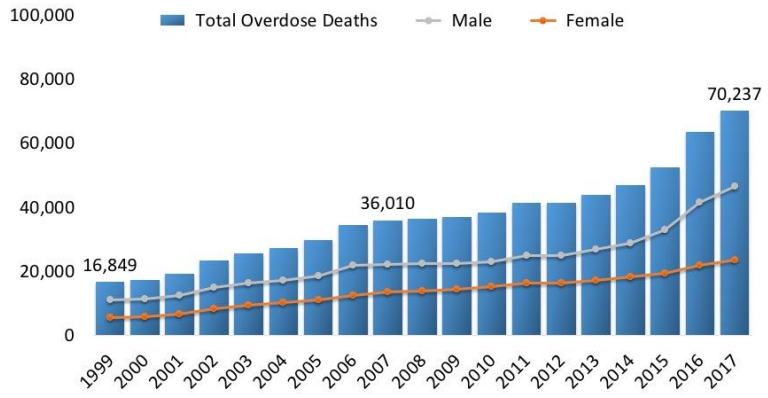
Mother Morphine (i.e. any opioid) certainly promises to soothe both physically and psychologically but she also has a fierce and barbed hook. She exacts a price for any continuous demand for her. North America began to pay that price. Prices for 'Oxy' sold on the street were high as prescription charges apply in the US and huge demand from those with poorly controlled habits. Ironically heroin was far cheaper. You see where this is going now don't you?

Black tar heroin is a crude version of heroin very different to the brown heroin that dominates the UK market or white heroin found in Scandinavia, which are more refined and generally better quality. It originates in Latin America and mostly services the western and southern US. One of its names is Mexican Tar Heroin. More and more dependent OxyContin users who otherwise would have been unlikely to use any form of heroin started to switch to it, and crucially, to injecting it. It was cheap, it was available.

At a policy level OxyContin was then seen for what it is; the antecedent and driver of the 'Opioid Crisis' sweeping North America. The rate of fatal overdoses climbed steeply, from 16,849 in 1999 to 70,237 in 2017 (Figure 1 below). Of the 2017 deaths, 47,600 (or 68%) involved an opioid. The Centres for Disease Control and Prevention (CDC) issued far stricter guidelines for prescribing of

opioids for non-cancer pain. It has been argued that while this should prevent far fewer new people developing a habit, it may push the already dependent OxyContin users to the illicit opioid market.

Figure 1. **National Drug Overdose Deaths**
Number Among All Ages, by Gender, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

The fentanyls have arrived?

In the UK we have also seen rising rates of fatal overdoses, and a similar proportion of them involve an opioid. However we quite rightly focus primarily on the dangers of mixing drugs rather than the risks of any one particular drug. The accidental or deliberate ingestion of alcohol, opioids, benzodiazepines, sedating antihistamines and gabapentinoids are very risky. Other factors such as the route(s) of administration to the body, duration of effect, potency, potentiating adulterants, dosing, timing of dose(s) and whether users are alone or not are also very important.

You might have spotted an odd sounding phrase in the last sentence; potentiating adulterants. Adding a 2nd drug to another drug mixture to make the effects stronger. The end user rarely knows this has happened. From a suppliers point of view they want to maintain their market share and decreasing purity of the drug they sell is rarely good for business. Add a little something extra not to bulk it out but to make up for the poor quality. And if that something else only needs to be a few grains so much the better.

That's what happened to the black tar heroin in the US. First with fentanyl which is 50-100 times stronger than morphine and then other fentanyls such as carfentanil which is 10,000 times stronger. I had some minor surgery a number of years ago which required a general anesthetic. Being interested in these things I asked the anesthetist what he planned to use. ''Propofol and alfentanil'' he replied. Michael Jackson had only recently died after his doctor had given him propofol (among other drugs). The mixture knocked me out at a count of only 3.

It only takes a small amount of a fentanyl in the batch of black tar heroin to make it stronger. Therefore you don't have the problem of shipping a barrel load from China. A couple of kilos will do. And that is easy to send undetected. The problem is the mixing process. If the heroin and fentanyl are unequally mixed throughout the batch there will be stronger and weaker parts of it. It's the stronger parts which are more likely to cause overdose. It is also known that it is more difficult to get an even mix of a fentanyl in black tar heroin due to its stickier consistency that other forms. Therefore in reality it is hard to end up with a homogeneous mixture as only few grains more of a fentanyl, in any particular part of the mix, means that part is particularly potent.

In May 2017 I spoke at a conference in Vancouver. We dip tested used empty but used heroin spoons (known as cookers) for fentanyl. Every single one showed fentanyl had been used. 18 months later in New Orleans, at another conference, we did the same thing but tested for both heroin and fentanyl. Most of the spoons had no heroin on them. But ***all*** had fentanyl. If these crude results are indicative of all North America it means that many if not all heroin users are now using fentanyl instead, wittingly or unwittingly.

Widespread naloxone distribution and Drug Consumption Rooms (DCRs) across the US and Canada try to hold back the tide of death by overdose. They will do that in many cases and a lot else besides but they won't be able to stop all of the deaths. Much more radical reforms will be needed, especially of drugs policy which is still rooted in a criminal justice framework and an explicit effect of a 'war on drugs'. A shift to a health focus, a regulated drugs market, a determined attempt to eradicate poverty are far more ambitious than even DCRs

and naloxone distribution but are even more effective medicines against overdose.

The UK

Why have we not seen anywhere near as much fentanyl within the UK's heroin supply? Our own heroin is more refined and better quality, on average, than that in the US. Therefore it makes little sense for a dealer to risk killing his or her punters with a fentanyl. There have been small clusters of fentanyl deaths in the north of England but none from contaminated heroin this side of the Irish Sea. The vast majority of deaths involving a fentanyl are those using fentanyl patches for pain. Not from using them as directed for 72 hours on the skin but from extracting it from the patch in one of a number of ways. Deaths involving fentanyl in NI have been 13 in 2017 and 10 in 2018. All were from extraction of fentanyl from patch formulations, none were from fentanyl powders contaminating heroin or other drugs. We think. However a recent Advisory Council on the Misuse of Drugs report cautions that UK deaths involving fentanyls are 'likely to be under-represented, since sufficiently detailed forensic analyses are not always carried out' ACMD (2020). In light of that we should remain open to the possibility that a fentanyl has been involved in an apparent heroin overdose until testing can prove otherwise.

"There are fewer younger people using drugs in the UK than the same age group 10 years ago", the Home Office proudly announces. However this figure masks that 34% of 8,238 drug deaths across the EU occurred in the UK (EMCDDA, 2019) with sharp rises in each of the 4 nations and in particular, in Scotland. Less people using drugs but more harms experienced by those that do. There are many factors which could explain these mortality figures; an aging cohort of drug users (the so called 'Trainspotting generation'), higher risk drug users not engaging in treatment or excluded from it (particularly in GB) and prescription drug use alongside illicit substance use (especially in NI). The lack of DCRs and only limited drug checking/testing facilities and very few Heroin Assisted Treatment schemes also play their part. Some also say that an apathy at Home Office level to radically overhaul the Misuse of Drugs Act is fair comment.

In Northern Ireland we saw a 39% rise in all drug related deaths from 2017 to 2018. Of the total number of deaths (n=189); 115 or 61% involved 1 or more opioids. Worryingly, deaths involving heroin almost doubled in 1 year, from 24 to 40. If you live in an area of severe deprivation, have poor mental health, are male, aged between 25 and 34 you have a hugely incresed risk of becoming one of those sad statistics. Although the number of deaths in 2019 will not be published until early 2021, I would bet they will again be a huge rise, based on my observations and that of my Extern colleagues. The fact that the data for 2019 will not be available until early 2021 does not help us identify risky trends at an early enough stage to risk to those still living who use substances. But that is a whole other story.

50 years since Nixon

With all the above said, what is abundantly clear is that the US led 'War on Drugs' has strongly influenced UK policy and legislation, and still does. It should not be a huge surprise then if we have similarities in our overdose profiles. Two major similarities between us are that most involve an opioid and the mixing of 2 or more substances (known as 'polydrug use'). What is different is the rate of drug related deaths are thankfully much lower in the UK generally than in the US. Another difference is that the higher prevalence of prescription medications being involved in NI deaths (such as exemplified by pregabalin being involved in 54 deaths in 2018 from only 9 in 2016). With these differences noted we should rightly focus on **polydrug use rather than be misdirected by the hype around a fentanyl, or any other drug for that matter**. If we target our efforts on that we may start to reduce the number of drug overdoses this side of the pond.

Chris Rintoul

Drugs and Alcohol Consultancy Service (DACS) by Extern / Northern Ireland Alcohol and Drugs Alliance (NIADA)

Campbell JN. APS 1995 Presidential address. Pain Forum. 1996; 5: 85–8.

Centres for Disease Control and Prevention
https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

National Institute on Drug Abuse https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

American Journal of Public Health 2009 February; 99(2): 221–227
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/

NISRA 2020 *Drug Related and Drug Misuse Deaths 2008-18*
https://www.nisra.gov.uk/publications/drug-related-and-drug-misuse-deaths-2008-2018

EMCDDA 2019 *Drug-related deaths and mortality in Europe*
http://www.emcdda.europa.eu/system/files/publications/11485/20193286_TD0319444ENN_PDF.pdf

ACMD 2020 *Fentanyl and Fentanyl Analogues*
https://www.gov.uk/government/publications/misuse-of-fentanyl-and-fentanyl-analogues